I. AMENDMENTS TO THE SPECIFICATION

Please amend the specification as shown:

Please insert the following on page 1, after the priority paragraph:

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on December 9, 2011, is named 26730006.txt and is 35,596 bytes in size.

Please delete the paragraphs on page 5, line 18 to page 6, line 3 and replace them with the following paragraphs:

It is further object of the present invention the use of an inhibitor of h-PRUNE cyclic nucleotide phosphodiesterase activity which is the peptide comprising the following amino acid sequence: NIIHGSDSVESAEKE (SEQ ID No 9). In a particularly preferred embodiment, said peptide also comprises, downstream of the aforementioned amino acid sequence, a further peptide liable of the permeability and having the sequence GGGYGRKKRRQRRR **(SEQ ID NO: 13)**. Therefore, the peptide characterised in that it is permeable, includes the following sequence NIIHGSDSVESAEKEGGGYGRKKRRQRRR (SEQ ID No 10).

It is a further object of the present invention the peptide comprising the following amino acid sequence:
NIIHGSDSVESAEKE (SEQ ID No 9) and in a particular embodiment the peptide comprising the following amino acid sequence:
NIIHGSDSVESAEKEGGGYGRKKRR[[O]]QRRR (SEQ ID No 10); and characterised in that it is permeable because of the final 14 amino acids in the sequence.

Please delete the paragraph on page 8, lines 28-33 and replace it with the following paragraph:

In addition the present invention pertains to a h-PRUNE (A59) rabbit polyclonal antibody characterised in that it recognises and binds selectively the peptide used for the rabbit immunization comprising the amino acid sequence: NH_2-A[[I]]<u>I</u>a-Leu-Glu-Glu-A[[I]]<u>I</u>a-Val-A[[I]]<u>I</u>a-Glu-Val-Leu-Asp-His-Arg-Pro-Ile-Glu-Pro-Lys-COOH (SEQ ID No 4) or parts thereof.

Please delete the paragraph on page 9, lines 17-24 and replace it with the following paragraph:

figure 1 shows multiple alignment of DHH family phosphoesterases sequences **<u>(SEQ ID NOS 15-117, respectively, in order of appearance, reading the figure from left to right from "Motif 1" to the "Specific motifs")</u>**, showing separately the four generic motifs (I-IV) and the motifs diagnostic of the two distinct subfamilies mapping to the second domain; numerals indicate the positions of the first aligned residue in each protein sequence and distances between the different elements (panel A). "Ribbon" structure of the hPRUNE protein based on the crystal structure of PPASE and the RecJ protein (panel B) and "ribbon" structure of the RecJ protein (panel C); the arrows indicate aspartic acids residues (D);

Please delete the paragraph on page 11, lines 19-36 and replace it with the following paragraph:

figure 11, A, shows *in vitro* immuno-precipitation of baculovirus produced h-PRUNE protein and Casein Kinasi δ *in vitro* phosphorylated and not phosphorylated nm23H1, several single mutations in S120-125 region were produced in order to show the complex formation through *in vitro* immuno-precipitation. The proteins are visible by Western blots

using anti-HIS antibodies present in terminal NH2 of the recombinant proteins synthesised in Baculovirus. Lane 1 and 2 shows recombinant proteins as control. Immuno-precipitations were performed with A-59 anti-h-prune polyclonal antibody and the detection by W.B. with anti-His tag (prune/nm23) polyclonal antibodies; figure 11 B shows protein sequence **(SEQ ID NO: 11)** and MALDI-MS of the protein, phosphorylation-positive serines are in bold type; figure 11 C shows COS7 expressed nm23-H2 using pcDNA-HA-nm23H2 construct and anti-HA recognising antibodies, following SDS page gel purification and trypsinization and sent to MALDI-MS molecular weight profile analysis, the identification of peptides and molecular mass thereof was carried out using Voyager mass-spectrometer with a mass increase corresponding to one or two phosphorylations. (80 Daltons, 160 Daltons);

Please delete the paragraph on page 25, lines 5-11 and replace it with the following paragraph:

For western blot analysis, 15 μg of protein lysate in buffer were analysed by SDS-PAGE on 10 % (w/v) or 12.5 % (w/v) polyacrylamide gels and were electroblotted onto a PVDF membrane (Immobilon-P, Millipore). The lysates were immuno-detected with h-PRUNE specific polyclonal (A59, raised against the motif III region) for h-PRUNE, nm23-H1 (clone NM301, specific for the H1 isoform; Santa Cruz) for nm23-H1 and Penta-His **(SEQ ID NO: 118)** against a His-tag (QIAGEN) for PDE5A antibodies, respectively.

Please delete the paragraph on page 51, lines 12-26 and replace it with the following paragraph:

The K73 polyclonal antibody was obtained using as immunogen a N115 to E127 phosphopeptide, phosphorylated in position S122, from nm23-H1 protein, the antiserum was used after IgG purification on the column of the resultant protein A in a non selective antibody and further affinity purification on the phosphopeptide (NIIHGSDSVKSAE **(SEQ**

ID NO: 14)) used as immunogen. This second procedure was carried out through cross-linking of 1 mg of desalted phospholipid dissolved in DMSO with the Affi-gel 25 resin (biorad) according to the manufacturer protocol. The coupled resin then was used for the affinity purification using serum of rabbit immunised with the phosphorylated and already purified and IgG peptide enriched (K73 polyclonal antibody), directly applied on Affigel bound peptide column, up to the antibody was adsorbed by the column. The column was washed for each column ml with 10 ml of 100 mM Tris-HCl, pH 8, 10 ml of 500 mM NaC, 10 mM Tris-HCl, pH 8, 10 ml of 10 mM Tris-HCl, pH 8, respectively. Elution was conducted with 0,1 M glycine, pH 3.

Please delete the paragraphs on page 54, lines 6-29 and replace them with the following paragraphs:

The obtained results show that by inhibiting the Casein Kinase 1 δ using IC261 it is possible to inhibit nm23-H1 and H2 phosphorylation and therefore the bonding with h-prune protein *in vivo*. By using this drug it is possible therefore to inhibit the formation of the h-prune-nm23 complex, being this last dependent on phosphorylations in 8120, 8122, 8125 region (NIIHG**S**D**S**VE**S**AEKE **(SEQ ID NO: 9)**) by Casein Kinase I. This study allows to use IC261 for inhibiting the binding of nm23H1 and H2 to h-prune and inhibiting cellular motility induced by the protein complex.

A new procedure can foresee the use of new peptides permeable in the cell and competitive for the binding of h-prune, poaching quota of in vivo phosphorylated nm23-H1 and H2, whose sequence derives from the amino acidic sequence of nm23-H1 and H2 range of 8120, 8122 and 8125 serines (example H1: NIIHGSDSVESAEKE **(SEQ ID NO: 9)** followed by the permeable peptide sequence of the region of the HIV TAT protein; GGGYGRKKRRQRRR **(SEQ ID NO: 13)**; 95% of purity synthesized by PRIMM). Such or similar peptides are able to compete with Casein Kinasi I phosphorylation *in vivo*, on the H1 and H2 wild type proteins and reduce quota of phosphorylated nm23 responsible for h-prune complex formation and increase of h-prune cAMP-PDE activity in the cell and finally

induction of the cellular motility. Also a control peptide with recognition sequence of the Casein Kinasi I cramble referred as (H1-: SDEIGKVSENIAHSE **(SEQ ID NO: 12)** followed by permeable peptide sequence GGGYGRKKRRQRRR **(SEQ ID NO: 13)**) was synthesised. Using this technology it is possible to target more specifically the inhibition of interaction between h-prune and nm23 *in vivo*.